REMARKS

The Advisory Action dated December 23, 2009, indicates that Applicants' Amendment dated November 24, 2009, was not entered because Applicants' claims contain non-elected subject matter. Although Applicants believe entry of the previously offered amendments were consistent with their request for joinder, Applicants now submit a Request of Continued Examination and accordingly request entry and examination of the amended claims. Applicants note in this regard that their claims are further limited to embodiments in which R^1 is hydrogen, C_1-C_8-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, or C_1-C_6-haloalkyl and in which R^3 is limited to C_1-C_8-alkyl or C_1-C_8-haloalkyl. The amendment of Claim 20 has necessitated cancellation of dependent Claim 26, as well as the amendment of dependent Claim 24.

With respect to the definitions of R^1 and R^3, Applicants gratefully acknowledge the Examiner's reminder in the Advisory Action about the scope of examination as it relates to R^3 and further note that similar comments could have been made about R^1. See Office Action dated December 29, 2008, at pages 3-4, which pointed out that the scope of the searched subject matter included embodiments in which, inter alia, R^1 is hydrogen or C_1-C_8-alkyl and R^3 is C_1-C_8-alkyl. Applicants' amended claims are directed to embodiments in which R^1 is hydrogen or C_1-C_8-alkyl, as well as the closely related groups C_1-C_4-alkoxy-C_1-C_4-alkyl or C_1-C_6-haloalkyl, and in which R^3 is C_1-C_8-alkyl, as well as the closely related group C_1-C_8-haloalkyl. Applicants respectfully submit that such groups would not add an undue burden on examination and request that they be included within the embodiments under consideration. Applicants also again request joinder of withdrawn Claim 31.

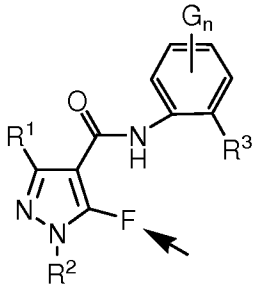
Applicants gratefully acknowledge the clarification in the Final Office Action that text appearing at page 11 of the previous Office Action was to be ignored and further acknowledge the withdrawal of the written description rejection of Claim 30 under 35 U.S.C. 112, first paragraph. The following arguments are essentially those presented in the Amendment that was not entered.

Rejection under 35 U.S.C. 103

Claims 20, 21, 24, 27, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over DE 10136065 by Elbe et al ("the '065 publication") (which, as previously noted by Applicants, is a German language document corresponding to published US 2004/0204470, listed in Applicants' Form PTO 1449) in view of the

teaching of bioisosterism in the cited article by Patani et al, *Chem. Rev.*, 96, 3147-3176 (1996). Applicants respectfully traverse.

As fully discussed in Applicants' Amendment dated May 28, 2009, the '065 publication discloses pyrazolylcarboxanilides having the formula



in which **R**^{1} is hydrogen, cyano, halogen, nitro, (halo)alkyl, cycloalkyl, (halo)alkoxy, (halo)alkylthio, or aminocarbonylalkyl; **R**^{2} is hydrogen, (halo)alkyl, alkenyl, cycloalkyl, (halo)alkylthioalkyl, or (halo)alkoxyalkyl; **R**^{3} is unsubstituted C_2-C_{20}-alkyl, C_1-C_{20}-alkyl that is mono- or polysubstituted by halogen or cycloalkyl, or optionally halogen- or cyclohexyl-substituted alkenyl or alkynyl; **G** is halogen or alkyl; and **n** is 0, 1, or 2. E.g., '065 publication at page 1, line 16, through page 2, line 17. Applicants again point out that a critical feature of such compounds is a fluorine substituent at the 5-position of the pyrazole ring (as shown by the arrow, where the 5-position numbering is that used in the reference for compound names). Applicants' claimed compounds, in contrast, never have a fluorine at the pyrazole 5-position. Applicants therefore maintain that the '065 publication would not itself suggest their invention.

Applicants also maintain that the Patani et al article would not lead those skilled in the art to their claimed invention. Applicants at the outset gratefully acknowledge the Examiner's observation that their previous explanation of the data in Figure 11 (Table 9) was flawed. However, upon inspection of the data reported in the reference, Applicants submit that the data in Table 9, when correctly interpreted as discussed below, actually bolster their position that the Patani et al article teaches inconsistent results that would not lead those skilled in the art to a predictable general conclusion about fluorine substitution.

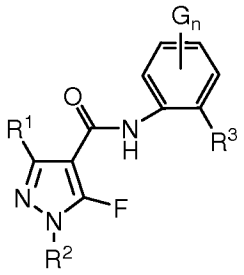
The Patani et al article beginning at page 3149 discusses several examples of bioisosterism relating to fluorine substitution, including some examples showing the interchangeability of hydrogen and fluorine (e.g., pages 3149-3150) and other examples showing the effect of replacing hydrogen with fluorine, hydroxyl, amino, or

methyl groups (e.g., pages 3152-3155). However, examination of the Patani et al article clearly reveals that significant and unpredictable differences in biological activity can arise when making such changes. For example (as correctly discussed in Applicants' previous Amendment), **Figure 2 (Table 4)** shows an almost four-fold greater binding affinity (as shown by a lower inhibitory concentration IC_{50}) when H is replaced by F in one naphthyl-fused diazepine but an almost twenty-fold greater binding affinity for a second naphthyl-fused diazepine. **Figure 3 (Table 5)** shows about 2.6 times greater anti-inflammatory activity for a difluoro androstane derivative compared to the monofluoro analog but only about 1.5 times greater activity for a related monofluoro androstane derivative compared to the dihydro analog having no fluoro substituent. Since both of the monofluoro compounds shown in Figure 3 have almost the same activity, one might expect that going from no fluorine to one fluorine and from one fluorine to two fluorines would result in a uniform increase in activity for each additional fluorine, but this was not the case. Instead, in contrast to the dramatic increase in activity shown in Figure 2, only modest changes in activity are shown in Figure 3, but in each case the activities increase with fluorine substitution. **Figure 11 (Table 9)**, when correctly analyzed as kindly pointed out by the Examiner, actually bolsters Applicants' position. That is, in contrast to the increased biological activity found for the compounds shown in Figures 2 and 3, the fluorine-substituted test compound shown in Figure 11 (Table 9) exhibited about 1.6 times lower angiotensin converting enzyme activity and about 2.4 times lower endopeptidase activity (as shown by greater inhibitory concentration IC_{50} in each test). In short, the data in Figure 2 (Table 4) and Figure 3 (Table 5) showed variably enhanced activity when F replaces H, whereas the data in Figure 11 (Table 9) showed reduced activity when F replaces H. That is, a proper reading of the Patani et al article shows that the specific degree of activity was both variable and unpredictable from compound to compound and from test to test. Therefore, even if one assumes that hydrogen can sometimes be replaced by fluorine or fluorine by hydrogen, that does not mean that one skilled in the art would be able to predict what activity (or level of activity) would result. Applicants therefore maintain that the '065 publication, whether taken alone or with the Patani et al article, would not lead those skilled in the art to their invention.

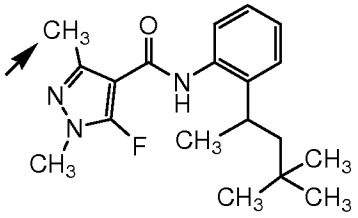
In further support of the patentability of their invention, Applicants previously submitted Declarations under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann

and Dr. Peter Dahmen showing that the inventive compound of their Example 6 exhibits unexpectedly superior efficacy at several application rates in three different antimicrobial tests compared with a corresponding fluorine-substituted compound falling within the general teachings of the '065 publication. Applicants again submit that those skilled in the art would not expect such differences in efficacy and thus would not be led by the cited references to their invention. The Final Office Action at pages 3-4, however, challenges the sufficiency of these tests because Applicants' tests did not use the previously cited compound (i.e., compound (I-1), shown at page 7 of the previous Office Action dated December 29, 2009) and did not use the same organisms as described in the '065 publication. Applicants submit that both criticisms are misplaced.

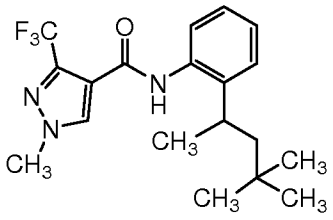
First, the previous Office Action at page 7 observes that the '065 publication discloses a compound having the general formula



(already shown above but shown again here for convenience of the Examiner) and describes as a specific example compound (I-1) having the formula

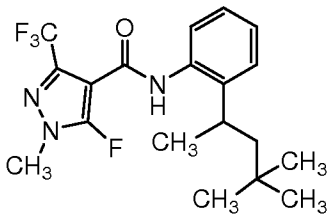


(where the arrow indicates a methyl substituent relevant to the current discussion). Mindful of their duty to compare closely related compounds, Applicants selected for comparison suitable pairs of compounds that were available when needed to overcome the rejections now at issue. One such compound was Applicants' compound of Example 6 having the formula



,

for which data were already reported in the current specification and which conveniently would be suitable for comparison with compounds of both the '065 publication and U.S. Patent 7,358,214 (discussed below with respect to an obviousness type double patenting rejection). However, this inventive compound has a trifluoromethyl substituent instead of a methyl group on the pyrazole ring. For the comparison experiments to have meaning, Applicants therefore selected for comparison an available trifluoromethyl-substituted compound having the formula



in which the only difference from the inventive compound of Applicants' Example 6 is fluorine substitution on the pyrazole ring. Although this compound is not specifically exemplified in the examples of the '065 publication, it clearly falls within the scope of the reference, which teaches that the trifluoromethyl group is among the preferred meanings of group R^1. See, for example, page 9, lines 7-8. Applicants submit that this trifluoromethyl- and fluorine-substituted compound is a fully acceptable comparison compound within the scope of the '065 publication, particularly since it differs from the compound of Example 6 of the invention only in having a fluorine substituent on the pyrazole ring.

Second, Applicants are not aware of any requirement that they must use a biological test described in a reference rather than any other relevant testing. Applicants chose three commonly used relevant antimicrobial tests, each of which showed that the compound of their invention exhibited superior results compared to the comparison compound. The Office Action provides no objective evidence that such tests are not properly probative.

Applicants therefore respectfully submit that their claimed invention is patentably distinct from DE 10136065 in view of the Patani et al article.

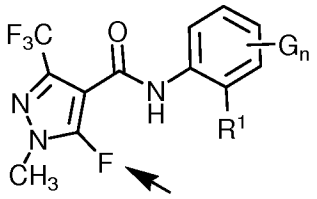
Double Patenting Rejections

Applicants claims stand rejected or provisionally rejected on the ground of nonstatutory obviousness-type double patenting based on several copending applications (one of which has issued).

A. U.S. Patent 7,358,214

Claims 20, 21, 24, 27, and 30 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-7 of U.S. Patent 7,358,214 ("the '214 patent"). Applicants respectfully traverse.

As fully discussed in Applicants' Amendment dated May 28, 2009, the '214 patent discloses and claims pyrazolylcarboxanilides having the formula



in which **R**^{1} is unsubstituted C_2-C_{20}-alkyl, C_1-C_{20}-alkyl that is mono- or poly-substituted by halogen or cycloalkyl, or optionally halogen- or cyclohexyl-substituted alkenyl or alkynyl; **G** is halogen or alkyl; and **n** is 0, 1, or 2. E.g., '214 patent at column 1, lines 15-42. A critical feature of such compounds is a fluorine substituent at the 5-position of the pyrazole ring (as shown by the arrow), a feature not found in Applicants' claimed compounds.

As fully discussed above with respect to the obviousness rejection based on DE 10136065 and the Patani et al article, the compound disclosed in Example 1 of the ' 214 patent is the compound used in the comparison experiments discussed above and is thus undisputedly comparative with Applicants' inventive compound of Example 6, which differs from the prior art compound only in not having a 5-fluoro substituent on the pyrazole ring. In view of the unexpectedly superior efficacy of Applicants' inventive compound of Example 6 at several application rates in three different antimicrobial tests, Applicants respectfully maintain that their claimed invention is fully distinguishable from the claims of the '214 patent.

Applicants acknowledge the observation in the Final Office Action at page 4 that an appropriate terminal disclaimer would overcome this rejection. However, Applicants maintain for the reasons discussed above that that terminal disclaimer

with respect to the '214 patent is not necessary and that their claimed invention is patentably distinct from the claims of the '214 patent.

B. Published US 2004/0204470

Claims 20, 21, 24, 27, and 30 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 22-35, 37, and 46 of copending US 2004/0204470 ("the '470 publication"). Applicants respectfully traverse.

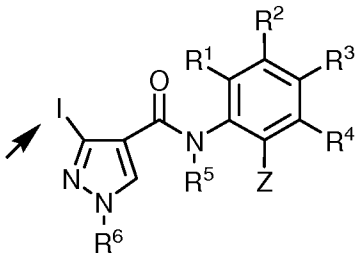
As pointed out in Applicants' Amendment dated May 28, 2009, the '470 publication is a counterpart of DE 10136065, upon which is based the obviousness rejection discussed above. For essentially the same reasons discussed above with respect to the obviousness rejection, Applicants submit that their claimed invention is patentably distinct from the '470 publication.

Applicants acknowledge the observation in the Final Office Action at page 4 that an appropriate terminal disclaimer would overcome this provisional rejection. However, Applicants maintain for the reasons discussed above that that terminal disclaimer with respect to the '470 publication is not necessary and that their claimed invention is patentably distinct from the claims of the ''470 publication.

C. Published US 2007/0066673

Claims 20, 21, 24, 27, and 30 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 11, 12, and 14 of copending US 2007/0066673 ("the '673 publication"). Applicants respectfully traverse.

As fully discussed in Applicants' Amendment dated May 28, 2009, the '673 publication discloses iodopyrazolylcarboxanilides of the formula



in which **R**^{1}, **R**^{2}, **R**^{3}, and **R**^{4} are independently hydrogen, fluorine, chlorine, methyl, isopropyl, or methylthio; **R**^{5} is hydrogen or any of a host of possible substituents; **R**^{6} is (halo)alkyl or alkoxyalkyl; and **Z** is optionally substituted phenyl, unsubstituted C_2-C_{20}-alkyl, C_1-C_{20}-alkyl that is mono- or polysubstituted by halogen or cycloalkyl,

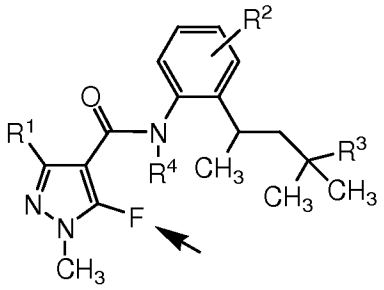
or optionally substituted alkenyl or alkynyl or Z and R^4 together can form an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring. E.g., paragraphs [0003] through [0019]. A critical feature of such compounds is iodine substitution at the 3-position of the pyrazole ring (as shown by the arrow), a structural feature not found in Applicants' claimed compounds.

Although Applicants believe that their claimed invention is patentably distinct from the '673 publication, Applicants would be willing to submit an appropriate terminal disclaimer as suggested in the Final Office Action if their claims are otherwise found allowable.

D. Published US 2007/0072930

Claims 20, 21, 24, 27, and 30 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 13-18 of copending US 2007/0072930 ("the '930 publication"). Applicants respectfully traverse.

As fully discussed in Applicants' Amendment dated May 28, 2009, the '930 publication discloses pyrazolylcarboxanilides of the formula



in which **R^1** is methyl, trifluoromethyl, or difluoromethyl; **R^2** is hydrogen, fluorine, chlorine, methyl, or trifluoromethyl; **R^3** is hydrogen, halogen, or (halo)alkyl; and **R^4** is any of a host of possible substituents, some of which are dependent on whether R^3 is hydrogen or is halogen or (halo)alkyl. E.g., paragraphs [0003] through [0015]. A critical feature of such compounds is fluorine substitution in the pyrazole ring (as shown by the arrow), a feature not found in Applicants' claimed compounds.

As discussed above with respect to the obviousness rejection based on DE 10136065 in view of the Patani et al article, Applicants have shown the inferiority of compounds of this type having a 5-fluoro substituent on the pyrazole ring. Applicants believe that their data, though indirectly relevant, support their position that their claimed invention is patentably distinct from the 'reference. Nevertheless,

Applicants would be willing to submit an appropriate terminal disclaimer as suggested in the Office Action if the claims are otherwise found allowable.

Objection to the Claims

Claims 21, 24, 27, and 30 remain objected to a being dependent on rejected Claim 20. For the reasons broadly discussed above, Applicants submit that they have traversed this objection.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

Respectfully submitted,

By _____

Richard E. L. Henderson
Attorney for Applicants
Reg. No. 31,619

Bayer CropScience LP
2 T.W. Alexander Drive
Research Triangle Park, NC 27709
Ph: 919-549-2183
Fax: 919-549-3994
Q:patents/prosecution documents/cs8774/8774 amendment 1-26-10